UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,299	08/20/2004	Jacob Waugh	13720-105110US1	3791

65989 7590 09/23/2009

KING & SPALDING
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-4003

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
09/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/505,299	WAUGH ET AL.	
	Examiner	Art Unit	
	KENDRA D. CARTER	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-68,70,72-76,78 and 80-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-68,70,72-76,78, and 80-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of June 26, 2009 made to the office action filed December 26, 2008. Claims 44-68, 70, 72-76, 78, and 80-85 are pending. Claims 44, 56, 62, 68, 70, 74, 75, 76, 78, 82 and 83-85 are amended.

In light of the amendments, the following rejections are withdrawn: 1) the 35 U.S.C. 112, first paragraph rejection of claims 44-67, 71, 74, 79, 83, 84, 85, 70 and 78; and 2) the 112, second paragraph rejection of claims 70, 78 and 82.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 USC 112, first paragraph rejection of claims 74 and 82, and all previous 35 U.S.C. 103(a) rejections were found not persuasive, thus the rejection is upheld.

Due to the amendment to the claims and withdrawal of several rejections, the modified and new 35 USC 103(a) and 112, first paragraph rejections are made below. Applicant's arguments are addressed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 74 and 82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating wrinkles, does not reasonably provide enablement for the amelioration of fat atrophy or fat regression in the skin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of stabilizing or remodeling fat. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when

assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 74 is drawn to a "method according to claim 68, wherein said cosmetic effect is the amelioration of fat atrophy or fat regression in the skin."

(2) The breadth of the claims:

Claims 74 and 82 embraces and reads on all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin such as weight management and wrinkles. The specification does not enable the treatment of all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin.

(3) The state of the prior art:

The state of the art regarding treating all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin is very low or do not exist.

(4) The predictability or unpredictability of the art:

The predictability of knowing and then treating all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin is low. Therefore, to one skilled in the art, treating all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to treating all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that treating all conditions that would benefit from the stabilization or remodeling of fat. The specification teaches that vasodilation may lead to a lesser appearance of certain fine lines and wrinkles (see page 1, last paragraph, last 2 lines). The specification also teaches that fat stabilization, particularly in humans, is generally associated with the appearance of aging attributed to fat atrophy as well as fat regression in the skin (see page 9, last paragraph). The current specification reaches to all the conditions that exist and those that still have not been determined that relate to the treatment of the amelioration of fat atrophy or fat regression in the skin, with no enablement or prior art for all of these conditions. Note that lack of a working

example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02.

(7) The quantity of experimentation necessary:

The instant claims read on the treatment of all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin. As discussed above the specification fails to provide any support for treating all conditions that would benefit from the amelioration of fat atrophy or fat regression in the skin. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

Particularly, the skilled practitioner would have to test L-arginine polymer to determine treatment efficacy for each condition. For example, to test for treatment of the disease, a particular compound having vasodilating activity would have to be selected, and a suitable animal model and dosage regimen (dose amount, frequency, route of administration) would also have to be selected. If efficacy of the drug did not result, the dosage regime would have to be varied, for example by changing the dosage amount or route of administration, until efficacy was achieved. If no animal model of a

condition is available for testing, then toxicity trials would have to be conducted before such testing could be conducted in humans to determine appropriate toxicity levels. If efficacy in the treatment of the condition was shown with the particular compound, then another compound having vasodilating activity would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Once efficacy was established for all or a representative sample of the compounds as claimed for treating the amelioration of fat atrophy or fat regression in the skin, the process would have to be repeated. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate each compound having vasodilating activity for the treatment of the amelioration of fat atrophy or fat regression in the skin, in order to be able to fully carry out the invention commensurate in scope with the claims.

Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for treating wrinkles, but not for treating the amelioration of fat atrophy or fat regression in the skin.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(1) Claims 44-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fossel (US 5,895,658), in view of Cooke et al. (US 6,605,115 B1), in further view of, Rothbard et al (U.S. Patent Application Publication No. 2002/0009491).

Fossel teaches that a topical (see column 1, lines 1-3) composition comprising an effective amount of L-arginine as the main substance to relax the blood vessels and thus permitting enhancement of blood flow to the tissue (see abstract, lines 1-8 and claim 1), to achieve beneficial effects such as warning cold tissue, growth of hair on the scalp, as well as restoration of natural mechanisms based on improvement of local blood supply (see column 1, line 8-14; addresses claims 44, 48 and 60). L-arginine is a precursor to the molecule nitric oxide, NO, being transformed into NO and citruline by the enzyme nitric oxide synthetase. Nitric oxide is the substance that relaxes the blood vessels, allowing for increased blood flow (i.e. vasodialator; see column 2, lines 66-67 to column 3, lines 1-3). L-arginine, in its various forms, may be contained in a variety of

topical preparations such as creams (see column 4, line 4 and see column 2, lines 18-20; addresses claims 44 and 61), emulsions, liposomes, collagen peptides, other components of skin (i.e. additional skin care or skin repair/skin barrier repair actives), or a vehicle such that L-arginine would prefer to be in tissue (i.e. cosmetically or dermatologically acceptable vehicle; see column 3, line 41-44 and 55; 44, 49; addresses claims 50, 53, 54, 62 and 64). In regards to the properties of the components of skin being additional skin care, skin repair or skin barrier repair actives, one can not separate the property from the compound. Increased lipid, oil and/or wax content is encouraged (i.e. natural or synthetic oils; see column 3, line 53; addresses claims 52 and 66). The formulation can further comprise other active agents, such as other agents that can be used which are also precursors or donors of nitric oxide including L-arginine, alkyl esters of L-arginine and salts such as hydrochloride, glutamate, butyrate, and glycolate (see column 3, lines 24-33; addresses claims 51 and 63).

Fossel does not specifically teach the following: 1) a polymer having from 7 to 15 subunits of L-arginine (claims 44-47 and 57-59); 2) the polymer further comprising a hydrophobic, hydrophilic, or amphipathic moiety, or a second polymer, linked or anchored to a terminal L-arginine subunit of the polymer (claims 55 and 67); and 3) the polymer further consisting of one or more additional amino acid other than L-arginine (claim 56).

Regarding claims 44 and 56, it is noted that, for the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, the transitional phrase "consisting essentially of' is being construed as equivalent to "comprising," absent a clear indication in the specification or claims of what is meant by, i.e. what is being excluded from the composition by, the phrase "consisting essentially of." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355, and MPEP 2111.03. The above applies to all the rejections below.

Cooke et al. teaches a method of increasing nitric oxide (NO) production in a vascular cell or tissue by contacting a polymer consisting of from 6 to about 30 amino acid subunits such as 7 to 15 L-arginine residues (i.e. Applicant's compound; see column 4, lines 12-18 and claim 26; addresses claims 44-47 and 56-59). The arginine oligomers were found to be significantly more efficacious than equivalent amounts of free arginine monomers, which is not significantly taken up by the walls of the arterial and venous segments (see column 10, lines 17-20). The (L)-arginine oligomers enhance NO production by supplementing intracellular (L)-arginine levels (see column 10, lines 26-38).

Rothbard et al. teaches providing compositions for enhancing the delivery of drugs and other agents across a biological barrier, such as skin, the composition employing a delivery enhancing transporter, such as a poly-arginine molecule that is

between 6 and 50 residues in length (see abstract, in particular.) Rothbard teaches that examples of such delivery enhancing transporters can comprise from 7 to 15 amidino moieties, such as heptamers, octamers, nonamers and the like of arginine (see paragraph 0048, in particular.) Rothbard et al. furthermore teaches that the amino acids can be L amino acids (see paragraph 0055, in particular.) Rothbard et al. teaches that the compositions comprising the polyarginine molecule can comprise a conventional pharmaceutical carrier and can be formulated for topical administration in a suitable format, such as a lotion (see paragraphs 0128 and 0134, in particular). Rothbard et al. furthermore teaches that small organic molecule agents can be combined with the transporters to facilitate or enhance transport (see paragraph 0076, in particular.) Rothbard et al. teaches that such compounds can include small organic molecules that have poor solubilities in aqueous liquids (see paragraph 0076, in particular), and thus are hydrophobic.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the composition and method of Fossel and a polymer having from 7 to 15 subunits of L-arginine (claims 44-47 and 57-59), or consisting of one or more additional amino acid other than L-arginine (claim 56), because of the following teachings: 1) Fossel teaches that the L-arginine agent can be in its various forms (see column 4, line 4), and that the formulation can comprise other agents that can be used which are also precursors or donors of nitric oxide (see column 3, lines 24-33); 2) Cooke et al. teach polymer consisting of from 6 to about 30 amino acid subunits

such as 7 to 15 L-arginine residues increase nitric oxide (NO) production in a vascular cell or tissue (see column 4, lines 12-18 and claim 26); 3) Cooke et al. also teach that the arginine oligomers were found to be significantly more efficacious than equivalent amounts of free arginine monomers, which is not significantly taken up by the walls of the arterial and venous segments (see column 10, lines 17-20); and 4) Cooke et al. teach that the (L)-arginine oligomers enhance NO production by supplementing intracellular (L)-arginine levels (see column 10, lines 26-38). Thus, one skilled in the art would use the oligomers of (L)-arginine with or without other amino acids because they are better vasodiolators than the monomers.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the composition and method of Fossel in view of Cooke et al. and the polymer further comprising a hydrophobic, hydrophilic, or amphipathic moiety, or a second polymer, linked or anchored to a terminal L-arginine subunit of the polymer (claims 55 and 67) because of the following teachings: 1) Rothbard teaches that 7 to 15 amidino moieties, such as heptamers, octamers, nonamers and the like of arginine provide delivery enhancing transporters properties (see paragraph 0048); 2) Rothbard et al. furthermore teaches that small organic molecule agents can be combined with the transporters to facilitate or enhance transport (see paragraph 0076), which include small organic molecules that have poor solubilities in aqueous liquids (see paragraph 0076), and thus are hydrophobic; 3) the compositions of Fossel are desired to be hydrophobic to enhance delivery (see column

3, lines 39-67). Thus, one skilled in the art would further comprise hydrophobic moieties onto the polymer with expectations of providing a drug that is better delivered through the skin. While Rothbard et al., Fossel, or Cooke et al. do not specifically exemplify linking the biologically active agent to the side chain of the terminal L-arginine subunit, it is considered that one or ordinary skill in the art at the time the invention was made would have found it obvious to provide such an association, based on the ion pair teachings of Rothbard et al, with the expectation of providing a suitable transport pair for skin treatment.

Regarding independent claim 56, Rothbard et al. furthermore teaches that peptides comprising arginine in addition to other amino acid residues can also be used as the delivery-enhancing polymer, and furthermore teaches that the delivery-enhancing transporters of the invention can be flanked by, or interrupted by, one or even more than one non-guanidino/non-amidino subunits (such as glycine, alanine and cysteine), that do not significantly affect the rate of transmembrane transport of the delivery-enhancing compound compositions (see paragraphs 0048 and 0071, in particular.) Accordingly, Rothbard et al. teaches the polymer having contiguous arginine subunits, with a number of subunits that overlaps with the range claimed in claim 56, the polymer being flanked by one amino acid other than L-arginine, in which the L-arginine subunits would be situated at the C-terminus or the N-terminus of the polymer, as recited in claim 56. Rothbard et al. furthermore teaches providing a dermatologically acceptable carrier in combination with delivery-enhancing polymers, as discussed for claim 44 above, and

thus the composition recited in claim 56 is also obvious over the teachings of Rothbard et al.

(2) Claims 68, 70, 76, and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fossel (US 5,895,658), in view of Cooke et al. (US 6,605,115 B1), in further view of Rothbard et al (U.S. Patent Application Publication No. 2002/0009491).

Fossel teaches that a topical (see column 1, lines 1-3) composition comprising an effective amount of L-arginine as the main substance to relax the blood vessels and thus permitting enhancement of blood flow to the tissue (see abstract, lines 1-8 and claim 1), to achieve beneficial effects such as warning cold tissue, growth of hair on the scalp, as well as restoration of natural mechanisms based on improvement of local blood supply (see column 1, lines 8-14; addresses claims 68, 70, 76 and 78). L-arginine is a precursor to the molecule nitric oxide, NO, being transformed into NO and citruline by the enzyme nitric oxide synthetase. Nitric oxide is the substance that relaxes the blood vessels, allowing for increased blood flow (i.e. vasodialator; see column 2, lines 66-67 to column 3, lines 1-3). L-arginine, in its various forms, may be contained in a variety of topical preparations such as creams (see column 4, line 4 and see column 2, lines 18-20). The formulation can further comprise other active agents, such as other agents that can be used which are also precursors or donors of nitric oxide including L-

arginine, alkyl esters of L-arginine and salts such as hydrochloride, glutamate, butyrate, and glycolate (see column 3, lines 24-33; addresses claims 68 and 76).

Fossel does not specifically teach the following: 1) identifying a region of the body in need of cosmetic enhancement (claims 68 and 76); 2) a polymer having from 7 to 15 subunits of L-arginine (claims 68 and 76); 3) increase in length or thickness of eyelashes or eyebrows (claims 70 and 78); 4) the polymer further consisting of one or more additional amino acid other than L-arginine , providing that the L-arginine subunits are contiguous and situated at either the C-terminus or the N-terminus of the polymer (claim 76).

Cooke et al. teaches a method of increasing nitric oxide (NO) production in a vascular cell or tissue by contacting a polymer consisting of from 6 to about 30 amino acid subunits such as 7 to 15 L-arginine residues (i.e. Applicant's compound; see column 4, lines 12-18 and claim 26). The arginine oligomers were found to be significantly more efficacious than equivalent amounts of free arginine monomers, which is not significantly taken up by the walls of the arterial and venous segments (see column 10, lines 17-20). The (L)-arginine oligomers enhance NO production by supplementing intracellular (L)-arginine levels (see column 10, lines 26-38).

Rothbard et al. teaches providing compositions for enhancing the delivery of drugs and other agents across a biological barrier, such as skin, the composition

employing a delivery enhancing transporter, such as a poly-arginine molecule that is between 6 and 50 residues in length (see abstract, in particular.) Rothbard teaches that examples of such delivery enhancing transporters can comprise from 7 to 15 amidino moieties, such as heptamers, octamers, nonamers and the like of arginine (see paragraph 0048, in particular.) Rothbard et al. furthermore teaches that the amino acids can be L amino acids (see paragraph 0055, in particular.) Rothbard et al. teaches that the compositions comprising the polyarginine molecule can comprise a conventional pharmaceutical carrier and can be formulated for topical administration in a suitable format, such as a lotion (see paragraphs 0128 and 0134, in particular). Rothbard et al. furthermore teaches that small organic molecule agents can be combined with the transporters to facilitate or enhance transport (see paragraph 0076, in particular.) Rothbard et al. teaches that such compounds can include small organic molecules that have poor solubilities in aqueous liquids (see paragraph 0076, in particular), and thus are hydrophobic.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the composition and method of Fossel and a polymer having from 7 to 15 subunits of L-arginine (claims 68 and 76), or consisting of one or more additional amino acid other than L-arginine (claim 76), because of the following teachings: 1) Fossel teaches that the L-arginine agent can be in its various forms (see column 4, line 4), and that the formulation can comprise other agents that can be used which are also precursors or donors of nitric oxide (see column 3, lines 24-33); 2)

Cooke et al. teach polymer consisting of from 6 to about 30 amino acid subunits such as 7 to 15 L-arginine residues increase nitric oxide (NO) production in a vascular cell or tissue (see column 4, lines 12-18 and claim 26); 3) Cooke et al. also teach that the arginine oligomers were found to be significantly more efficacious than equivalent amounts of free arginine monomers, which is not significantly taken up by the walls of the arterial and venous segments (see column 10, lines 17-20); and 4) Cooke et al. teach that the (L)-arginine oligomers enhance NO production by supplementing intracellular (L)-arginine levels (see column 10, lines 26-38). Thus, one skilled in the art would use the oligomers of (L)-arginine with or without other amino acids because they are better vasodiolators than the monomers.

Regarding independent claim 76, Rothbard et al. furthermore teaches that peptides comprising arginine in addition to other amino acid residues can also be used as the delivery-enhancing polymer, and furthermore teaches that the delivery-enhancing transporters of the invention can be flanked by, or interrupted by, one or even more than one non-guanidino/non-amidino subunits (such as glycine, alanine and cysteine), that do not significantly affect the rate of transmembrane transport of the delivery-enhancing compound compositions (see paragraphs 0048 and 0071, in particular.) Accordingly, Rothbard et al. teaches the polymer having contiguous arginine subunits, with a number of subunits that overlaps with the range claimed in claims 68 and 76, the polymer being flanked by one amino acid other than L-arginine, in which the L-arginine subunits would be situated at the C-terminus or the N-terminus of the polymer, as recited in claim 76.

Thus, one skilled in the art would be motivated to make a derivative of the L-arginine composition of Fossel in view of Cooke with the expectation of providing a vasodilator with enhancing transporter properties.

In regards to identifying a region of the body in need of cosmetic enhancement (claims 68 and 76), Fossel obviously teaches this limitation because Fossel teaches that the composition produces beneficial effects through restoration of natural mechanisms based on improvement of local blood supply (see column 1, lines 11-13). Thus, when one wants to impart the above treatment, one skilled in the art would identify and then apply the composition to the parts of the body that would benefit from restoration of natural mechanisms to provide a therapeutic and/or cosmetic change.

In regards to the cosmetic effect not being a promotion of hair growth, the method provides other beneficial results such as healing leg ulcers, warming cold tissue and other beneficial effects through restoration of natural mechanisms based on improvement of local blood supply (see column 1, lines 11-13).

In regards to increase in length or thickness of eyelashes or eyebrows (claims 70 and 78), one skilled in the art would find it obvious and motivated to apply the composition of Fossel in view of Cooke et al. and Rothbard et al. because Fossel teaches that the composition is effective in growing hair and restoring natural mechanisms based on improvement of local blood supply (see column 1, lines 8-14).

Thus, upon increasing the blood flow to the eyelash or eyebrow region, one would increase nutrients that are needed to promote growth of the hair.

(3) Claims 72 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fossel (US 5,895,658), in view of Cooke et al. (US 6,605,115 B1) and Rothbard et al (U.S. Patent Application Publication No. 2002/0009491) as applied to claims 68, 70, 76, and 78 above, in further view of Frome (US 5,571,794 A).

Fossel, Cooke et al. and Rothbard et al. are as applied above to claims 68, 70, 76 and 78.

Fossel, Cooke et al. and Rothbard et al. do not teach the specific cosmetic effects of lip plumpness, change in lip color, or lip contour.

Frome teaches a method to achieve an enlargement of the lips by applying a composition comprising a topical vasodilator (see abstract; column 2, lines 23-46).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Fossel in view of Cooke et al. and Rothbard et al. to provide lip plumpness or contour because Frome teaches that topical application of vasodilators enlarge the lips. Therefore, the topical vasodilator

composition of Fossel in view of Cooke et al. and Rothbard et al. would be expected to provide effective lip plumpness due to increased blood flow to the lips.

(4) Claims 74, 82, 84 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fossel (US 5,895,658), in view of Cooke et al. (US 6,605,115 B1) and Rothbard et al (U.S. Patent Application Publication No. 2002/0009491) as applied to claims 68, 70, 76, and 78 above, in further view of Gazzani (US 5,053,230).

Fossel, Cooke et al. and Rothbard et al. are as applied above to claims 68, 70, 76 and 78.

Fossel, Cooke et al. and Rothbard et al. do not teach wherein the cosmetic effect is that disclosed in claims 74, 82, 84 or 85.

Gazzani teaches that when blood circulation towards and within the germinative layer is hindered, or the feeding of nutrient substances is reduced (which is known that feeding takes place by blood circulation), the layer becomes more and more atrophied and the skin becomes wrinkled and old-looking, while hair follicles lack the capacity for forming new hair (see column 1, lines 25-40).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Fossel in view of Cooke et al. and Rothbard et al. and wherein the cosmetic effect is that disclosed in claims 74, 82, 84 or 85 because of the following teaching: (1) Cooke et al. teach that the applicant's compound increases the production of nitric oxide; (2) Fossel teaches that a topical composition of L-arginine increases the blood flow to a tissue to achieve growth of hair (see column 1, lines 1-5); and (3) Gazzani teaches that when blood circulation towards and within the germinative layer is hindered, or the feeding of nutrient substances is reduced (which is known that feeding takes place by blood circulation), the layer becomes more and more atrophied and the skin becomes wrinkled and old-looking, while hair follicles lack the capacity for forming new hair (see column 1, lines 25-40). Thus, upon increasing the blood circulation with an L-arginine oligomer to the skin, the tissue area will regain nutrients and blood to reduce wrinkles and the look of old age (i.e signs of aging, loss of skin firmness, loss of skin tightness, loss of skin recoil, amelioration of fat atrophy or fat regression in the skin).

(5) Claims 73 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fossel (US 5,895,658), in view of Cooke et al. (US 6,605,115 B1) and Rothbard et al (U.S. Patent Application Publication No. 2002/0009491) as applied to claims 68, 70, 76, and 78 above, in further view of Kligman (US 4,877,805 A)

Fossel, Cooke et al. and Rothbard et al. are as applied above to claims 68, 70, 76 and 78.

Fossel, Cooke et al. and Rothbard et al. do not teach wherein the cosmetic effect is to enhance sensitivity to skin.

Kligman teaches that retinoids increase vascularity, which stimulate blood flow and promote the formation of new vessels. Blood flow is greatly reduced in aged, sundamage skin. A brisker blood supply improves the physiologic competence of the skin and imparts a livelier, glowing appearance, in which the patients often say their skin feels "more alive" (i.e. increased sensitivity; see column 5, lines 34-40).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method and composition of Fossel in view of Cooke et al. and Rothbard et al. and a method to enhance skin sensitivity because Kligman teaches that by increasing blood flow through a vasodiolator, the skin is livelier and feels more alive. Further, Fossel teaches that the L-arginine composition warms cold tissue (see column 1, lines 8-14). Thus, upon increasing the blood circulation with an L-arginine oligomer to the skin, one skilled in the art would expect the tissue area to become more sensitive and give the patient a feeling of being more alive.

(5) Claims 75 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fossel (US 5,895,658), in view of Cooke et al. (US 6,605,115 B1) and Rothbard et al (U.S. Patent Application Publication No. 2002/0009491) as applied to claims 68, 70, 76, and 78 above, in further view of Lohinai et al. (Med Sci Monit, 1998, vol. 4, issue 6, pp. 1089-1095).

Fossel, Cooke et al. and Rothbard et al. are as applied above to claims 68, 70, 76 and 78.

Fossel, Cooke et al. and Rothbard et al. do not teach wherein the cosmetic effect is a transient enlargement of gums.

Lohinai et al. teach that the excess of NO (i.e. nitric oxide) in the gingivomucosal tissue is responsible for the gingival swelling (see page 1092, column 2, lines, first paragraph).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method and composition of Fossel in view of Cooke et al. and Rothbard et al. and a method to create a cosmetic effect of transient enlargement of gums because of the following teachings: (1) Cooke et al. teach that the applicant's compound increases the production of nitric oxide; and (2) Lohinai et al. teach that the excess of NO (i.e. nitric oxide) in the gingivomucosal tissue is responsible

for the gingival swelling (see page 1092, column 2, lines, first paragraph). Thus, one would be motivated to use the claimed compound to enlarge the gums because it is known in the art that excess NO gives this effect.

Response to Arguments

Applicant's arguments have been fully considered but they are not all persuasive. Applicant's arguments with respect to the withdrawn rejections and amendments to the claims have been considered but are moot in view of the new ground(s) of rejection.

> The Applicant argues that Fossel and Cooke teach away from the claimed invention. Particularly, Cooke reports that only in situation of "vascular injury" or trauma were local L-arginine concentrations depleated, would the supplementation of extracellular aginine polymers be expected to increase NO syntehesis (see Cooke, col. 9, page 48-58). Thus, Cooke teaches away from the present invention, because it suggests that L-arginine polymers would not cause vasodilation if used for cosmetic purposes. Fossel discourages the skilled artisan from topically applying L-arginine polymers for cosmetic purposes, by suggesting that the penetration ability of L-arginine polymers would be expected to be quite low.

The Examiner respectfully disagrees, and notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Fuller provides the teaching that a topical composition of L-arginine increases the blood flow

to a tissue for cosmetic use (see column 1, lines 1-5). Fuller also teaches that the formulation can further comprise other active agents, such as other agents that can be used which are also precursors or donors of nitric oxide including L-arginine (see column 3, lines 24-33). Thus, the polymer can be used as taught by Cooke et al. Cooke et al. provides the teaching that arginine oligomers were found to be significantly more efficacious than equivalent amounts of free arginine monomers, which is not significantly taken up by the walls of the arterial and venous segments (see column 10, lines 17-20). Cooke et al. also teaches that the (L)-arginine oligomers enhance NO production by supplementing intracellular (L)-arginine levels (see column 10, lines 26-38). Thus, one skilled in the art would use the oligomers of (L)-arginine with or without other amino acids because they are better vasodiolators than the monomers. Even though Cooke et al. teaches vascular injury, one can not separate the property of the compound. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case or either anticipation or obviousness has been established. Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Therefore, Fuller provides the teaching of the monomer used in cosmetic art, whereas Cooke et al. provides the motivation for one skilled in the art to use the polymer over the monomer.

> The Applicant argues that the Examiner has made impermissible changes in the principle of operation of both Cooke and Rothbard. Cooke is for the prevention of migration and proliferation of smooth muscle cells in the vasculature. Further Rothbard is directed to the use of charged polymers, such as polyarginine, for the delivery of therapeutic agents.

Again, the Examiner respectfully disagrees, and notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The primary reference is Fuller, which provides the teaching of L-arginine being used to produce a cosmetic or/and therapeutic effect. Cooke et al. and Rothbard is used to provide teaching of the properties of the polymer and motivation for using the polymer over the monomer.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. D. C./
Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617